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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)	
	10/650,057	VON KNEBEL DOEBERITZ ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *7-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed November 15, 2006, is acknowledged and has been entered.

2. Claims 1-18 are pending in the application. Claims 7-18 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Claims 1-6 are currently under prosecution.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment

5. The amendment filed on November 15, 2006, is considered non-compliant because it fails to meet the requirements of 37 CFR § 1.121, as amended on June 30, 2003 (see *68 Fed. Reg. 38611*, Jun. 30, 2003). However, in order to advance prosecution[1], rather than mailing a Notice of Non-Compliant Amendment, Applicant is advised to correct the following deficiency in replying to this Office action:

The amendment is non-compliant because it replaces two paragraphs at page 3, beginning in line 24, without showing the changes that have been made relative the immediate prior versions of those paragraphs.

For clarity, the changes that have been made to these paragraphs corrects the typographical error that was noted in section 8 at page 4 of the preceding Office action, but otherwise the text of the brief descriptions of the respective figures has not been altered.

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[1] See M.P.E.P. § 714.03.

37 CFR § 1.121 provides for amendments to the specification that are limited to the substitution of existing paragraphs by amended versions thereof, provided that the changes that have been made relative to their immediate prior versions are marked in the prescribed manner, the insertion of new paragraphs, and the deletion of entire paragraphs from the disclosure. Not provided for by the rule are amendments to the specification made by deleting an entire paragraph, only to replace it with an amended version without showing how the original version of the paragraph has been changed.

Only the corrected section of the non-compliant amendment must be resubmitted (in its entirety), e.g., the entire "Amendments to the specification" section of applicant's amendment must be re-submitted. 37 CFR § 1.121(h).

Priority

6. Applicant has identified Application No. 10/633,484 as containing a certified copy of European Patent Office Application No. 02017313.4.

7. As noted in the preceding Office action mailed August 16, 2006, claims 1-6 do not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed, since the specification of earlier filed U.S. Patent Application No. 09/743,103 does not describe the claimed method, which comprising the step of *solubilizing the cervical body sample in a lysis buffer* before determining the overexpression of cyclin dependent kinase inhibitor p16.

Furthermore, claim 4 does not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed, since the specification of earlier filed U.S. Patent Application No. 10/633,484 does not describe the method according to claim 4, wherein the determination of the level of cyclin dependent kinase inhibitor p16 in a healthy human cervical sample is *carried out once for each lot of detection reagents*.

Accordingly, the effective filing date of present claims 1-3, 5, and 6 is deemed the filing date of U.S. Patent Application No. 10/633,484, namely July 31, 2003; whereas

the effective filing date of claim 4 is the filing date of the instant application (i.e., August 26, 2003).

Grounds of Objection and Rejection Withdrawn

8. Unless specifically reiterated below, Applicant's amendment and/or arguments filed November 15, 2006, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed August 16, 2006.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 102

9. The rejection of claims 1 and 3-6 under 35 U.S.C. 102(e), as being anticipated by U.S. Patent No. 6,709,832 B1, as evidenced by Geradts et al. (*Am. J. Pathol.* 1999 Jun; **154** (6): 1665-1671), is maintained.

Beginning at page 5 of the amendment filed November 15, 2006, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that Von Knebel Doeberitz et al. does not teach solubilizing the cervical body sample and detecting the overexpression of p16 in the solubilized sample. The Examiner disagrees.

As explained in the preceding Office action, Von Knebel Doeberitz et al. does not expressly teach the process by which the overexpression of p16 is determined comprises lysing the cells and solubilizing the protein. Nonetheless, Von Knebel Doeberitz et al. teaches the determination is made by Western blot analysis, a process briefly described by Example 2 at column 4, lines 55-67, *which involves the preparation of cell extracts*; and as evidenced by Geradts et al., **the determination of the overexpression, which is made by Western blot, comprises the step of lysing the cells and solubilizing the protein to be detected**; see entire document (i.e., the preparation of cell extracts), particularly page 1666, column 2.

Applicant has further argued that the methodology that is disclosed by Von Knebel Doeberitz et al. is exemplified in Example 2, which demonstrates the use of this methodology to detect p16 in HPV-transformed cells, not in a solubilized cervical body sample.

In response, the examples set forth in the disclosure by Von Knebel Doeberitz et al. are merely exemplary, and are not intended to limit the nature of the sample of cells that is used in practicing the disclosed process.

As explained in the preceding Office action, Von Knebel Doeberitz et al. teaches a method for detecting cervical carcinomas, cervical intraepithelial neoplasias, or cervical carcinomas *in situ*; see entire document (e.g., the Abstract; the disclosure at column 2, lines 15-22; the Examples at columns 3-5; claim 1). According to the disclosure, the process comprises determining the overexpression of cyclin-dependent kinase inhibitor p16 in a human cervical body sample by comparing the expression level of cyclin-dependent kinase inhibitor p16 within said sample to the expression level present in a healthy human cervical body sample; see, e.g., column 4, Table 1; claim 1). The human cervical body sample is selected from a blood sample, a smear, a sputum sample, urine, bone marrow, an organ punctuate or aspirate, a biopsy, a preserved cytological or histological specimen, and a fixed cell or tissue preparation; see, e.g., column 2, lines 33-40; column 3, line 35, through column 4, line 66. The determination of the overexpression is made by any of various methods, including in particular Western blot, ELISA, and immunoprecipitation; see, e.g., column 2, lines 51-56. Again, as evidenced, for example, by the teachings of Geradts et al., it is submitted that these particularly noted methods for determining the overexpression would be immediately be understood by the artisan to involve the step of solubilizing the proteins present in the cells or tissues of the samples.

Applicant has argued that Example 2 set forth as part of the disclosure of Von Knebel Doeberitz et al. does not show the detection of p16 in "a mixed native cell population".

In response, the claims are directed to a method for detecting cervical carcinomas, cervical intraepithelial neoplasia, or cervical carcinomas in situ by a

process that comprises the step of determining the overexpression of p16 in a cervical body sample, not "a mixed native cell population". Again, as noted above, Von Knebel Doeberitz et al. teaches a method for detecting cervical carcinomas, cervical intraepithelial neoplasias, or cervical carcinomas *in situ* by a process that comprises determining the overexpression of p16 in a cervical body sample.

Applicant has remarked that Geradts et al. does not "add anything to the '832 patent".

Geradts et al. is cited to provide factual evidence that the determination of the overexpression, which is made by Western blot, comprises the step of lysing the cells and solubilizing the protein to be detected. Von Knebel Doeberitz et al. teaches a method for detecting cervical carcinomas, cervical intraepithelial neoplasias, or cervical carcinomas *in situ* by a process that comprises determining the overexpression of p16 in a cervical body using a Western blot analysis. Accordingly, as evidenced by Geradts et al., Von Knebel Doeberitz et al. teaches a method for detecting cervical carcinomas, cervical intraepithelial neoplasias, or cervical carcinomas *in situ* by a process that comprises solubilizing the cervical body sample in a lysis buffer and then determining the overexpression of p16 in the solublized sample.

Applicant has remarked that the claims are directed to a method where "native cells" are solublized.

In response, the claims do not recite the term "native cells".

Applicant has further remarked, "there is no pre-selection of cells to enrich or sort out cell types to facilitate the p16 detection" (page 6, paragraph 5, of the amendment filed November 15, 2006).

In response, it is of no consequence whether or not there is pre-selection of cells to enrich or sort out cell types to facilitate the p16 detection. The limitations of the claims have been met.

Applicant has remarked that the specification describes that practicing the invention as claimed provides the practitioner with an unexpected advantage.

In response, it is of no consequence whether or not the specification describes that practicing the invention as claimed provides the practitioner with an unexpected advantage. The limitations of the claims have been met.

Finally, at page 7 of the amendment, Applicant has contended that they were the first to discover that the measurement of a single marker, namely p16 in a lysate containing various different cell types in unknown ratios is an indication of cervical carcinoma.

In response, Von Knebel Doeberitz et al. teaches a process for detecting cervical carcinomas, cervical intraepithelial neoplasias, or cervical carcinomas *in situ*, which anticipates the claimed invention.

Claim Rejections - 35 USC § 103

10. The rejection of claim 2 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,709,832 B1, as evidenced by Geradts et al. (*Am. J. Pathol.* 1999 Jun; **154** (6): 1665-1671), in view of Ryder et al. (*Clin. Chem.* 1988 Dec; **34** (12): 2513-2516), is maintained.

At page 7 of the amendment filed November 15, 2006, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that the invention of claim 2 is not obvious for the same reasons that Von Knebel Doeberitz et al. does not anticipate the inventions of claims 1 and 3-6.

This argument is not persuasive because Von Knebel Doeberitz et al. teaches that which is set forth in the above rejection of claims 1 and 3-6 under 35 U.S.C. 102(e), and while Von Knebel Doeberitz et al. does not expressly teach the level of cyclin dependent kinase inhibitor p16 is provided as a predetermined value to set up a threshold for the detection procedure, Ryder et al. teaches predetermining the appropriate cut-off or decision threshold for use in diagnostic applications, which are based upon the measurement of a marker in bodily samples.

Therefore, it would have been obvious to one ordinarily skilled in the art at the time the invention was made to predetermine the appropriate cut-off or decision threshold for use in practicing the method described by Von Knebel Doeberitz et al. because Ryder et al. teaches predetermining the appropriate cut-off or decision threshold for use in diagnostic applications, which are based upon the measurement of a marker in bodily samples. One ordinarily skilled in the art at the time the invention was made would have been motivated to predetermine the appropriate cut-off or decision threshold for use in practicing the method described by Von Knebel Doeberitz et al. in order to reduce the number of false-positives and/or false-negatives to determine the presence of cervical carcinomas, cervical intraepithelial neoplasias, or cervical carcinomas *in situ* in patients with confidence and accuracy.

11. The rejection of claims 1 and 3-6 under 35 U.S.C. 103(a), as being unpatentable over Khleif et al. (*Proc. Natl. Acad. Sci. USA.* 1996 Apr; **93**: 4350-4354), as evidenced by Bio-Rad Protein Assay[2] (instruction manual provided with a Bradford assay kit manufactured by Bio-Rad) and the American Type Culture Collection™ (ATCC) catalog[3], in view Klaes et al. *(Int. J. Cancer.* 2001; 92: 276-284) (of record; cited by Applicant), is maintained.

At page 8 of the amendment filed November 15, 2006, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that Khleif et al. does not teach the overexpression of p16 in cervical carincoma cells.

In response, as noted in the preceding Office action, Khleif et al. teaches a process comprising obtaining a cervical body sample from a human subject (i.e., cervical cancer cells supplied by the American Type Culture Collection, such as HeLa cells), lysing the cells in a lysis buffer, clearing the lysates by centrifugation, and

[2] See http://www.fhcrc.org/science/labs/hahn/methods/biochem_meth/biorad_assay.pdf

determining the overexpression of the thus solubilized $p16^{INK4a}$ in the prepared samples; see entire document (e.g., the abstract; page 4350, column 2; page 4351, column 1 and Figure 1; and page 4343, column 1).

As evidenced by Bio-Rad Protein Assay, the protein must be solublized before a determination of the concentration of the protein may be made; see entire document, particularly page 11, item #6.

As evidenced by the ATCC catalog, the cervical cancer cells obtained by Khleif et al., such as HeLa cells, for example, were derived from a sample of an adenocarcinoma of the cervical epithelium of a human subject.

Khleif et al. does not however teach or expressly suggest determining the overexpression of cyclin-dependent kinase inhibitor p16 in a human cervical body sample by comparing the expression level of cyclin-dependent kinase inhibitor p16 within said sample to the expression level present in a healthy human cervical body sample. Furthermore, Khleif et al. does not however teach or expressly suggest acquiring cervical body samples selected from cytological smears, histological specimens, cervical swabs, biopsies, preserved cytological specimens, fixed cell or fixed tissue preparations. In addition, Khleif et al. does not however teach or expressly suggest the level of p16 in the healthy human cervical body sample is determined from a representative number of healthy human cervical samples.

Nevertheless, Klaes et al. teaches comparing the body sample to be examined with a corresponding body sample which originates from a healthy person; see entire document (e.g., the abstract; page 277, paragraph bridging columns 1 and 2; page 279, Table 1; page 282, column 2). Klaes et al. teaches acquiring cervical body samples selected from cytological smears, histological specimens, cervical swabs, biopsies, preserved cytological specimens, fixed cell or fixed tissue preparations; see, e.g., page 277, columns 1 and 2. Klaes et al. teaches the level of p16 in the healthy human cervical body sample is determined from a representative number of healthy human cervical samples; see, e.g., page 279, Table 1.

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[3] See http://www.atcc.com/catalog/numSearch/numResults.cfm?atccNum=CCL-2.

Therefore, given the combination of the teachings of the cited references, it would have been obvious to one ordinarily skilled in the art at the time the invention was made to practice the method for detecting cervical carcinoma cells according to the method described by Khleif et al. but determining the overexpression of cyclin-dependent kinase inhibitor p16 in a human cervical body sample (i.e., a cervical body sample selected from cytological smears, histological specimens, cervical swabs, biopsies, preserved cytological specimens, fixed cell or fixed tissue preparations) by comparing the expression level of cyclin-dependent kinase inhibitor p16 within the sample acquired from the subject to the expression levels present in representative number of human cervical body samples originating from healthy persons. One ordinarily skilled in the art at the time the invention was made would have been motivated to do so to more accurately determine the overexpression of p16 in the subject, as compared to the level of expression in a the cervical tissue of a healthy unaffected individual.

Applicant has argued that the sample of HeLa cervical carcinoma cells acquired by Khleif et al. was not taken from the body of a patient.

Applicant is incorrect; as evidenced by the American Type Culture Collection™ (ATCC) catalog, HeLa cervical carcinoma cells were acquired from the cervical epithelial adenocarcinoma of a 31 year old black female patient.

Applicant has argued that Khlief et al. does not teach the claimed invention.

In response to Applicant's arguments against any of the individual references, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Finally, Applicant has remarked that the secondary references do not remedy the insufficiency of the teachings of the primary reference.

In response, the Examiner disagrees, but notably Applicant has not pointed to any particular reason why the secondary references fail remedy the insufficiency of the teachings of the primary reference.

12. The rejection of claim 2 under 35 U.S.C. 103(a), as being unpatentable over Khleif et al. (*Proc. Natl. Acad. Sci. USA.* 1996 April; **93**:4350-4354) in view of Klaes et al. *(Int. J. Cancer.* 2001; 92: 276-284) (of record; cited by Applicant), as applied to claims 1 and 3-6 above, and further in view of Ryder et al. (*Clin. Chem.* 1988 Dec; **34** (12): 2513-2516), is maintained.

At page 8 of the amendment filed November 15, 2006, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has remarked that for the same reasons discussed in traversing the above rejection, this ground of rejection should be withdrawn.

In response, the Examiner disagrees.

As noted in the preceding Office action, while Klaes et al. and Khleif et al. teach that which is set forth in the above rejection of claims 1 and 3-6 under 35 U.S.C. 103(a), neither reference expressly teaches the level of cyclin dependent kinase inhibitor p16 is provided as a predetermined value to set up a threshold for the detection procedure; but nevertheless, Ryder et al. teaches predetermining the appropriate cut-off or decision threshold for use in diagnostic applications, which are based upon the measurement of a marker in bodily samples.

Therefore, it would have been obvious to one ordinarily skilled in the art at the time the invention was made to predetermine the appropriate cut-off or decision threshold for use in detecting the presence of dysplastic or neoplastic cervical cancer by determining the overexpression of p16 in a cervical sample acquired from a patient because Ryder et al. teaches predetermining the appropriate cut-off or decision threshold for use in diagnostic applications, which are based upon the measurement of a marker in bodily samples. One ordinarily skilled in the art at the time the invention was made would have been motivated to predetermine the appropriate cut-off or decision threshold for use in practicing the method in order to reduce the number of

false-positives and/or false-negatives to determine the presence of cervical lesions in patients with confidence and accuracy.

Double Patenting

13. The rejection of claims 1 and 3-6 on the ground of nonstatutory obviousness-type double patenting, as being unpatentable over claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 B1 in view of Khleif et al. (*Proc. Natl. Acad. Sci. USA.* 1996 Apr; **93**: 4350-4354), as evidenced by Bio-Rad Protein Assay[4] (instruction manual provided with a Bradford assay kit manufactured by Bio-Rad), is maintained.

At page 9 of the amendment filed November 15, 2006, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that the invention of claims 1 and 3-6 represent an improved process, not an obvious variant of the processes of claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 B1.

In response, the Examiner disagrees; and although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

As explained in the preceding Office action, claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 B1 are drawn to a method for detecting cervical carcinomas, cervical intraepithelial neoplasias, or cervical carcinomas *in situ*, said method comprising determining the overexpression of cyclin dependent kinase inhibitor p16 in a human cervical body sample selected from a smear, a organ punctuate, and a biopsy by comparing the expression level of the protein within the sample to the expression level of the protein present in a healthy human cervical body sample. According to claims 5, in particular, the overexpression of p16 is determined by detecting the protein in the sample by a process comprising reacting an antibody directed against the protein with the protein in the sample.

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[4] See http://www.fhcrc.org/science/labs/hahn/methods/biochem_meth/biorad_assay.pdf

In contrast to claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 B1, the instant claims are directed to detecting cervical carcinomas, cervical intraepithelial neoplasias, or cervical carcinomas *in situ* by a process comprising solubilizing the cervical body sample in a lysis buffer and then determining the overexpression of p16 in a human cervical body sample by comparing the expression level of cyclin-dependent kinase inhibitor p16 within said sample to the expression level present in a healthy human cervical body sample.

Khleif et al. teaches a process comprising obtaining a cervical body sample from a human subject (i.e., cervical cancer cells supplied by the American Type Culture Collection, such as HeLa cells), lysing the cells in a lysis buffer, clearing the lysates by centrifugation, and determining the overexpression of the thus solubilized $p16^{INK4a}$ in the prepared samples; see entire document (e.g., the abstract; page 4350, column 2; page 4351, column 1 and Figure 1; and page 4343, column 1).

As evidenced by Bio-Rad Protein Assay, the protein must be solublized before a determination of the concentration of the protein may be made; see entire document, particularly page 11, item #6.

Accordingly, it would have been obvious to one ordinarily skilled in the art at the time of the invention to have practiced the method according to claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 B1 by solubilizing the cervical body sample in a lysis buffer before determining the overexpression of p16 in a human cervical body sample by comparing the expression level of cyclin-dependent kinase inhibitor p16 within said sample to the expression level present in a healthy human cervical body sample.

14. The rejection of claim 2 on the ground of nonstatutory obviousness-type double patenting, as being unpatentable over U.S. Patent No. 6,709,832 B1 in view of Khleif et al. (*Proc. Natl. Acad. Sci. USA.* 1996 Apr; **93**: 4350-4354), as evidenced by Bio-Rad Protein Assay[5] (instruction manual provided with a Bradford assay kit manufactured by

[5] See http://www.fhcrc.org/science/labs/hahn/methods/biochem_meth/biorad_assay.pdf

Bio-Rad), as applied to claims 1, 2, 4, and 5 above, in further view of Ryder et al. (*Clin. Chem.* 1988 Dec; **34** (12): 2513-2516), is maintained.

At page 9 of the amendment filed November 15, 2006, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that the invention of claim 2 represents an improved process, not an obvious variant of the processes of claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 B1.

In response, the Examiner disagrees; and although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Although neither the claims of U.S. Patent No. 6,709,832 B1 nor Khleif et al. expressly teaches or suggests the level of cyclin dependent kinase inhibitor p16 is provided as a predetermined value to set up a threshold for the detection procedure, Ryder et al. nevertheless teaches predetermining the appropriate cut-off or decision threshold for use in diagnostic applications, which are based upon the measurement of a marker in bodily samples.

Therefore, it would have been obvious to one ordinarily skilled in the art at the time the invention was made to predetermine the appropriate cut-off or decision threshold for use in practicing the method of claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 B1 using methodology described by Khleif et al. because Ryder et al. teaches predetermining the appropriate cut-off or decision threshold for use in diagnostic applications, which are based upon the measurement of a marker in bodily samples. One ordinarily skilled in the art at the time the invention was made would have been motivated to predetermine the appropriate cut-off or decision threshold for use in practicing the method of claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 B1 using methodology described by Khleif et al. in order to reduce the number of false-positives and/or false-negatives to determine the presence of cervical carcinomas, cervical intraepithelial neoplasias, or cervical carcinomas *in situ* in patients with confidence and accuracy.

15. The provisional rejection of claims 1 and 3-6 on the ground of nonstatutory obviousness-type double patenting, as being unpatentable over claims 1-26, 33, 34, and 36-40 of copending Application No. 10/633,484 in view of Klaes et al. *(Int. J. Cancer.* 2001; 92: 276-284) (of record; cited by Applicant), is maintained.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

At page 9 of the amendment filed November 15, 2006, Applicant has expressed a wish to postpone the response to this provisional rejection until the claims are otherwise allowable.

16. As noted in the preceding Office action, claims 1 and 3-6 are directed to an invention not patentably distinct from claims 1-26, 33, 34, and 36-40 of commonly assigned copending Application No. 10/633,484. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth above in the provisionally rejection of the claims on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-26, 33, 34, and 36-40 of copending Application No. 10/633,484 in view of Klaes et al. *(Int. J. Cancer.* 2001; 92: 276-284) (of record; cited by Applicant).

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned copending Application No. 10/633,484, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

17. The provisional rejection of claims 1-6 on the ground of nonstatutory obviousness-type double patenting, as being unpatentable over claims 1-10, 14-16, 42-50, 52-57, and 85 of copending Application No. 10/569,758, is maintained.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

At page 9 of the amendment filed November 15, 2006, Applicant has expressed a wish to postpone the response to this provisional rejection until the claims are otherwise allowable.

18. As noted in the preceding Office action, claims 1-6 are directed to an invention not patentably distinct from claims 1-10, 14-16, 42-50, 52-57, and 85 of commonly assigned copending Application No. 10/569,758. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth above in the provisionally rejection of the claims on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 14-16, 42-50, 52-57, and 85 of copending Application No. 10/569,758.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned copending Application No. 10/569,758, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made

or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Conclusion

19. No claim is allowed.

20. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stephen L. Rawlings, Ph.D.
Primary Examiner
Art Unit 1643

slr
January 21, 2007